Antimalarial Drugs in Pregnancy: A Review

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Abstract: In this review we examine the available information on the safety of antimalarials in pregnancy, from both animal and human studies. The antimalarials that can be used in pregnancy include (1) chloroquine, (2) amodiaquine, (3) quinine, (4) azithromycin, (5) sulfadoxine-pyrimethamine, (6) mefloquine, (7) dapsone-chlorproguanil, (8) artemisinin derivatives, (9) atovaquone-proguanil and (10) lumefantrine. Antimalarial drugs that should not be used in pregnancy including (1) halofantrine, (2) tetracycline/doxycycline, and (3) primaquine. There are few studies in humans on the pharmacokinetics, safety and efficacy of antimalarials in pregnancy. This is because pregnant women are systematically excluded from clinical trials. The absence of adequate safety data, especially in the first trimester, is an important obstacle to developing treatment strategies. The pharmacokinetics of most antimalarial drugs are also modified in pregnancy and dosages will need to be adapted. Other factors, including HIV status, drug interactions with antiretrovirals, the influence of haematinics and host genetic polymorphisms may influence safety and efficacy. For these reasons there is an urgent need to assess the safety and efficacy of antimalarial treatments in pregnancy, including artemisinin based combination therapies.

Keywords: Pregnancy, malaria, antimalarial drugs, human studies, animal studies.

INTRODUCTION

For decades the prophylaxis and treatment of malaria during pregnancy have relied on chloroquine. Resistance in *P. falciparum* to chloroquine and increasingly to sulfadoxine-pyrimethamine in Africa, means that other antimalarials will have to be used in pregnancy on this continent, the worst affected by malaria. In South East Asia, multidrug resistance in *P. falciparum* emerged more than 30 years ago and drugs such as quinine, mefloquine, artemisinin derivatives and atovaquone-proguanil have been used to treat pregnant women with malaria. In this review we examine the available information on the safety of antimalarials in pregnancy, from both animal and human studies. The review is biased towards human studies, as most animal data is either unpublished or difficult to access. A literature search was performed using the PubMed data base and the name of each compound followed by "pregnancy", "animal studies" or "animal toxicity" were used as keywords. Published articles were located using previous reviews, and unpublished material was obtained from pharmaceutical companies and cited with permission.

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Chloroquine

This antimalarial has been extensively used in pregnancy but current use for treatment of *P. falciparum* malaria is greatly restricted due to parasite resistance. It is still used in some countries in West Africa and India but has largely been replaced by combination therapy in parts of S.E. Asia or by sulfadoxine-pyrimethamine in several countries in Africa. It remains a useful first-line drug for management of *P. vivax* malaria.

- Pre-clinical studies, animal data: In animals, chloroquine is associated with *in utero* effects on rat lungs at doses of 40 mg/kg near term [1] and on dendritic maturation of hippocampal neurons [2]. At high doses, chloroquine accumulates in eye and ear tissues [3].
- Human data on toxicity in pregnancy: The effects of 4 aminoquinolines in pregnancy have been well documented in patients treated for systemic lupus and

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rheumatoid arthritis, where doses up to 500 mg per day of hydroxycholoroquine were used [4,5]. These and more recent data [6] suggest that hydroxycholoroquine is safe in pregnant women with these systemic diseases. Although chloroquine is thought to be associated with a higher risk of retinal toxicity than hydroxycholoroquine [7,8], the experience with chloroquine as malaria chemoprophylaxis in pregnancy confirms that the drug may be used safely [9] even in the first trimester [10]. There are 755 cases of first trimester exposures to chloroquine in the published literature [9-16]. Chloroquine has been implicated in fetal toxicity in some reports [11,17] and recently, Massele *et al.* showed that the clearance of chloroquine was increased during the third trimester, and suggested that higher doses for prophylaxis should be studied, but the implications (if any) for treatment doses are unknown [18]. No increase in abortion risk (study powered to detect only large differences of ≥ 5%) was found with chloroquine treatment of 85 episodes of *P. vivax* (base 25 mg/kg over 3 days) in the 1st trimester (<13.0 weeks estimated gestational age), when compared to the community rate of abortion in 3,030 prospectively followed women who did not have malaria (18.3% and 17.8% respectively) [15].

- Clinical experience: Although chloroquine (25 mg base/kg) has been the drug of choice for the treatment of malaria in pregnancy for decades, the number of published studies on its efficacy and tolerability is limited. In 65 pregnant women treated in Kilifi hospital in Kenya (25 mg/kg divided over 3 days) *in vivo* tests showed that 46% of all the *P. falciparum* infections were resistant to chloroquine predominantly at RI and RII levels. The *in vitro* tests showed a resistance rate of 35% [19]. Mutabingwa *et al.* reported a good clinical response with chloroquine in 49 symptomatic semi-immune pregnant women in Tanzania in 1991. The dose was well tolerated, however 35% of women experienced a parasitological failure [20]. For as long as *P. falciparum* remained sensitive to chloroquine, the drug has been considered safe and effective in pregnancy [21]. The most common reported side effect in black Africans was pruritus [22]. Data on a further 634 women who received chloroquine base 25 mg/kg divided over 3 days, for treatment of *P. vivax* showed no decrease in mean gestational age, proportion of pregnancies ending in stillbirth, or abortion rates than the control group [23] .
- Usefulness of chloroquine in the context of drug resistance: resistance to chloroquine of *P. falciparum* is now established in almost all endemic countries. Consequently, the efficacy of chloroquine in the treatment of uncomplicated infection is unacceptably low [16,19,22,24-26]. Recently, Kublin *et al.* have reported re-emergence of chloroquine-sensitive *Plasmodium falciparum* after cessation of chloroquine use in Malawi, but the operational applicability of this observation requires multi-site studies. In contrast, chloroquine continues to be widely used in West Africa, even though chloroquine-resistant falciparum strains are increasingly prevalent. In the laboratory, *P. falciparum* resistance to chloroquine can be reversed by combining it with various drugs such as calcium inhibitors, phenothiazines, anti-depressants and anti-histamine compounds, but clinical evidence is limited and the usefulness of this approach in humans or pregnant women, has not been established.

Amodiaquine

Amodiaquine, like chloroquine is considered safe to use in pregnancy although there are virtually no data on its toxicity in pregnant women. Its use is severely limited by the cross resistance with chloroquine in *P. falciparum* but it can be used to treat non-falciparum malaria. It must not be used as prophylactic because of the risk of agranulocytosis.

- Pre-clinical studies, animal data: Amodiaquine is weakly mutagenic on Salmonella strains and is capable of inducing significant sister chromatid exchange (SCE) and chromosome aberrations *in vivo* in bone marrow cells of mice [27].
- Human data on toxicity in pregnancy: none in the published literature. In particular there is no reported case of first trimester exposure to amodiaquine.
- Clinical experience: published reports on the use of amodiaquine in pregnancy are scarce [28]. Steketee *et al.* treated 23 pregnant women who failed under chloroquine prophylaxis and reported a cure rate of 78% but no information was provided on adverse effects or on pregnancy outcomes [22]. A similarly limited report was published from Burma in 19 pregnant women with *P. falciparum* [29].
- Usefulness of amodiaquine in the context of drug resistance: probably limited by cross-resistance with chloroquine although studies in non-pregnant patients have shown that amodiaquine could retain efficacy even when resistance to chloroquine has emerged [30] and its combination with 3 days of artesunate could prove useful. A recent review on amodiaquine in pregnancy [31] concludes that there is an urgent need for studies on amodiaquine safety and tolerability during pregnancy since current data are not sufficient to recommend its use during pregnancy, particularly as intermittent treatment.

Quinine

Quinine is the oldest drug used to treat malaria and it remains widely used. It is especially valuable in the treatment of severe or drug resistant *P. falciparum* infections. It is considered to be safe during pregnancy although the evidence is limited and it is known to cause hypoglycaemia. it is not well tolerated and compliance to a full treatment course is poor. It cannot be used as a prophylactic.

- Pre-clinical studies, animal data: Quinine hydrochloride was not mutagenic in the Ames test using *Salmonella typhimurium* and showed no genotoxicity in hamsters, but demonstrated a dose-dependent increase in sister chromatid exchanges, and an enhanced incidence of micronuclei and elevated

chromatid breaks in mice [32]. Guinea pigs exposed antenatally to quinine developed abnormalities of the inner ear [33,34]. Eighth cranial nerve damage was also seen in the offspring of rabbits treated with quinine during pregnancy [35]. Other central nervous system defects may be seen in the offspring of treated rabbits and chinchillas [36]. In rats (>300 mg/kg/d) and rabbits (>100 mg/kg/d), the doses of quinine sulfate that were toxic for the fetus were also lethal for the pregnant animals, and 18 mg/kg of quinine provoked fetal death in 50% of treated dogs. Fetal abnormalities were not observed in any of the animals tested [37]. However, Lapoint and Nosal reported congenital malformations in 5% of pups born to rats receiving quinine sulfate in water (0.25 mg/ml) during pre-gestative and gestative periods, and mean birthweights were also significantly lower compared to pups born to control rats. Pups nursing on rats receiving quinine also demonstrated maturation retardation [38]. Colley *et al.* reported no teratogenic effects of quinine hydrochloride (up to 200 mg/kg/d from day 6 to 15) in Sprague-Dawley rats [39]. No fetal abnormalities or abortions were reported among 6 pregnant macaques given quinine hydrochloride (20-200 mg/kg daily) on days 27-29 of gestation [40].

- Human data on toxicity in pregnancy: Quinine has been (and still is) used as an abortifacient [41,43], although standard doses of quinine do not increase the risk of abortion [15,44]. Most concern on quinine safety has centred around the potential for auditory nerve damage [34,35,42,45-47] but there are also issues related to the association with hypoplasia of the optic nerve [48], and stillbirth when used for induction of labour [49]. An early critical review of the world literature by Winckel in 1948 suggested that there was little cause for concern and that the evidence for teratogenicity was circumstantial [50]. Since then, there have been only two published reports of quinine used for treatment of *P. falciparum* infection in the first 4 months of human pregnancy and no teratogenicity was detected in the 104 pregnant women treated [15,51]. Quinine was not associated with birth defects when used at therapeutic doses in 763 pregnant women among Karen refugees living on the Thai-Burma border [15,52,53]. No increase in uterine activity has been observed in women treated near term [54]. We found in the published literature, a total of 368 exposures to quinine in the first trimester [15,55,56] (see also F. Rosa cited in reference 57).

- Clinical experience: with the spread of chloroquine resistance, quinine has recovered its place as the first-line drug for treatment of falciparum infections in pregnancy. However, the number of clinical trials on the use of quinine in pregnancy is limited. At therapeutic doses, quinine is relatively well tolerated by pregnant women, but can cause hypoglycemia even in uncomplicated infections [58]. Recently, a large series was reported from Thailand where multi-drug resistance of *P. falciparum* is most severe. McGready *et al.* studied the efficacy and tolerability of supervised oral quinine (30 mg/kg/day for 7 days) in 178 Karen pregnant women with uncomplicated *P. falciparum* malaria attacks [59]. The most common drug-attributed adverse effects reported by the patients were tinnitus (35%) and dizziness (42%). Serious reactions or hypoglycemia were not observed. Parasitological and haematological responses were less than satisfactory: 4% of the women remained parasitemic by day 7 following the start of treatment, and 23% had recrudescences of malaria by day 28. More than 40% of the women treated became anaemic (haematocrit <30%) during the 4 weeks of follow-up. Since then, a separate study has used PCR genotyping to determine the true cure rate of quinine in pregnancy [53]. PCR genotyping allows a distinction to be made between recrudescent infection (or parasitological failures), and re-infection based on the malaria parasite genotype. In 41 women who received 7 days of supervised quinine (10mg/kg TID) for uncomplicated *P. falciparum* malaria in the 2nd and 3rd trimester of pregnancy, the cure rate was 67.0% (95% CI: 43.3-90.8%) by day 63. Interestingly, the genotyping confirmed recrudescence as late as 85 days (median [range] time to failure was 29 [21-85] days), even though the patient was microscopically negative on weekly smears in the intervening 3 months, most likely because of placental sequestration. This illustrates that the WHO standard *in-vivo* test is not adapted for pregnancy.

- Usefulness of quinine in the context of resistance: quinine is often combined with tetracyclines in non-pregnant patients in areas of multi-drug resistance, such as in South America and Southeast Asia, however tetracyclines are contra-indicated in pregnancy [60,61]. Spiramycin does not improve the efficacy of quinine [52], but clindamycin could be beneficial [62,63]. In 41 pregnant women with falciparum malaria on the Thai Burmese border followed weekly until delivery, quinine (30 mg/kg/day for 7 days) combined with clindamycin (15 mg/kg/day for 7 days) cured 65 (100%) recrudescent falciparum episodes in the 2nd and 3rd trimesters [64]. Although the efficacy was high, there was also a very high rate of gametocyte carriage 39 (95% CI: 21-66) per 1,000 person weeks. No congenital defects have been noted with the use of clindamycin [65,66]. No serious side effects and in particular, no *Clostridium difficile*-associated diarrhoea has been reported when clindamycin has been used as an antimalarial [64,66,67]. There were 1332 reported first trimester exposures to clindamycin in the literature of which 375 were exposed to clindamycin vaginal cream (F. Rosa cited in reference 57).

Azithromycin

This drug is not currently used as an antimalarial in pregnancy.

- Pre-clinical studies, animal data: azithromycin is an ideal anti-infective agent for use in pregnancy as it has a favourable safety profile although only a single

case of first trimester exposure is reported in the literature [70].

- Clinical experience: it is a slow acting and weak antimalarial against *P. falciparum* [71] and *P. vivax* [72]. It is less effective than clindamycin [72]. There were no published data identified on the use of azithromycin as an antimalarial in pregnant women. In non-pregnant patients, efficacy results are poor and only a limited number of patients have been studied: less than 200 for treatment of *P. falciparum*, less than 100 for treatment of *P. vivax*, and less than 600 cases for prophylaxis against *P. falciparum* or *P. vivax*.
- Usefulness in the context of drug resistance: antibiotics are slow acting antimalarials with parasite reduction ratios (PRR) of 5-10 per 48 cycle (Table **1**). Azithromycin should be used in conjunction with more effective antimalarials such as artemisinins and large doses of azithromycin may be required, making it less likely to be tolerated by pregnant women. The PRR of azithromycin is too slow for it to be partnered with a 3 day course of an artemisinin derivative.

Table 1. ***In Vivo*** **Pharmacodynamics of Antimalarials**

Antimalarial drugs	Estimated PRR *in vivo*[a]
Artemisinin, artesunate, artemether	10^3-10^5
4-Aminoquinolones, halofantrine	10^2-10^4
Quinine, mefloquine, pyrimethamine-sulfadoxine	10-10^3
Antimalarial antibiotics, desferrioxamine	5-10

[a]PRR = baseline parasite count/parasite count 48 hours later; this rises if there is background immunity and falls with resistance.

Sulfadoxine and Pyrimethamine [SP]

SP is used in pregnant women although the evidence for its safety is limited. Resistance in *P. falciparum* is spreading rapidly in Africa and well established in S.E. Asia and South America. SP is not suitable to use as a prophylactic drug and is ineffective against *P. vivax*.

- Pre-clinical studies, animal data: sulfonamides at low doses are not teratogenic in animals, but at high doses (100-1000 mg/kg/day) cause cleft palate in rats exposed from day 9 to 14 of gestation [73]. Pyrimethamine causes dose-dependent embryotoxicity in rats, but not at human equivalent doses [74]. At 50 mg/kg, pyrimethamine causes embryonic and maternal DNA changes related to folate deficiency [75]. The risk of embryotoxicity in rats is increased by the combination of pyrimethamine with folic acid, but is prevented by the use of folinic acid [76]. This is because folinic acid (5-methyl tetrahydrofolate) demethylation to form the active forms of folate (tetrahydrofolate) is not dependent on the enzyme dihydrofolate reductase which is inhibited by pyrimethamine. Folic acid reduction is dependent on this enzyme. In combination, sulfadoxine and pyrimethamine have shown a dose-dependent toxicity in rats [44]. At therapeutic doses of 0.72 mg/kg of SP intra-muscularly at day 5-12 and 19 of gestation in Wistar rats, complete embryo resorption was observed [77].
- Human data on toxicity in pregnancy: pyrimethamine (alone or as SP) has been used in pregnant women with toxoplasmosis, at doses up to 500 mg total dose without apparent toxicity for the mother and the fetus [44,78]. Sulfonamides were used as antibiotics in pregnancy and the rate of congenital abnormalities was not higher in 1455 women exposed to the drug in the first 4 months of pregnancy than in the general population [51]. One case-control study showed a higher exposure to sulfonamide among 134 mothers whose babies had cleft palate than among controls [79]. The sulfonamides compete with bilirubin for plasma proteins and can theoretically cause kernicterus in the premature fetus. However several studies have failed to demonstrate an increased risk of kernicterus following exposure to sulfonamides [78,80-83]. There were 286 cases of exposure to SP in the first trimester, and 26 to sulfones, and 1455 to sulfonamides identified in the literature [51,84-87].
- Clinical experience: for the treatment of uncomplicated *P. falciparum* malaria, the combination of sulfadoxine and pyrimethamine (SP) is prescribed increasingly as chloroquine-resistant strains spread, especially in Africa. Several published studies examined the use of SP (1500 mg of sulfadoxine and 75 mg of pyrimethamine) either to treat falciparum infections [22,25,88,89] or to prevent them [89,91], or both [90,92]. The concept of using serial treatment doses of SP to suppress malaria was studied by Lewis *et al.* in 1972 in pregnant and non-pregnant subjects in Malaysia [93]. Although the side effects of SP treatment were not usually reported in detail in these studies, SP appears to be well tolerated, the main adverse effects being rare (<3%) and limited to nausea, vomiting, rash, pruritus and fatigue [89]. The systematic administration during pregnancy of 2-3 doses of SP was particularly effective to prevent severe anaemia, an often under-recognized complication of malaria [91], but more doses are required to protect HIV-infected women from malaria and its complications [89]. None of these studies, involving a total of over 2000 pregnant women, detected an increased risk of malformations, kernicterus or any other severe effects on the fetus. The severe cutaneous reactions (toxic epidermal necrolysis and Steven Johnson syndrome) seen when SP is used as prophylaxis, have not been reported in treatment or intermittent preventive treatment (IPT), although HIV infected patients may be more at risk.
- Usefulness of SP in the context of resistance: Resistance to SP has emerged and quickly spread in several East African countries, raising concerns that resistance will spread across the entire continent [94]. *In vivo* efficacy studies in Malawi have shown comparable early treatment responses to sulfadoxine pyrimethamine in pregnant women and children who were studied at the same period of time and were from the same location. Parasite clearance by day 14 was 95% in both groups. In Nigeria only 30.7% of

pregnant women cleared their parasitaemia by day 14, compared to 14.7% of children [95]. The rapid decline of SP efficacy has triggered calls to use the artemisinin based combination therapies (ACT) outside pregnancy. However SP is still widely deployed alone for intermittent preventive therapy (IPT) during pregnancy, a strategy compromised by the spread of resistance. Pregnant women often carry gametocytes [96], possibly as a result of extended parasite carriage, and this could theoretically increase the transmission of resistant strains.

Mefloquine

Mefloquine is an effective antimalarial drug characterised by its long half life. It has been used widely in Asia and South America but the evidence for its safety in pregnancy is limited. Some authors recommend mefloquine as prophylaxis during pregnancy while others suggest a careful risk-benefit analysis in view of the known side effects of the drugs, and the possible increased risk of stillbirth.

- Pre-clinical studies, animal data: mefloquine causes skeletal and muscular malformations in rats at 5-20 times the therapeutic dose [97].
- Human data on toxicity in pregnancy: most of the available data comes from the post-marketing surveillance system of the manufacturer (F. Hoffman-La Roche) or case reports, focussing on the effects of mefloquine prophylaxis [84,98,99]. The analysis of these data, keeping in mind their limitations (retrospective studies, absence of controls, unknown denominator) does not support the hypothesis that mefloquine is associated with embryotoxicity, even in the first trimester [84]. Pharmacokinetic properties of mefloquine are slightly altered in pregnancy: the peak concentrations are lower and the apparent volume of distribution is larger [100] so that doses lower than 25 mg/kg may lead to sub-optimal circulating drug levels. There were 1271 cases of first trimester exposure to mefloquine identified in the literature of which 647 were from retrospective post marketing surveillance [16,55,56,84,98,99].
- Clinical experience: As for most antimalarials, few publications have reported on the use of mefloquine treatment in pregnancy. Harinasuta *et al.* treated 85 pregnant women with mefloquine and found no increase in adverse pregnancy outcomes [56]. Steketee *et al.* reported on the efficacy and the tolerability of mefloquine (750 mg) treatment followed by 250 mg weekly in over 1000 pregnant women in the 2nd and 3rd trimesters in Malawi. The drug was well tolerated and the main side effects were dizziness and gastrointestinal complaints. No deleterious effects on the fetus were noted [16]. Mefloquine (250 mg/week) for prophylaxis was effective and well tolerated in a double blind randomized trial in Karen women [101]. In Thailand, McGready *et al.* followed 279 Karen pregnant women in their last 2 trimesters and treated with mefloquine (25 mg/Kg) for uncomplicated multi-drug resistant *P. falciparum* infections. The main adverse effects of the drug were dizziness (36%) and anorexia (23%), but 6% of the women failed to clear their parasitaemia by day 7 and 28% had failed by day 42 following treatment [59]. In the same community, a retrospective study of 3587 pregnancies of which 208 were exposed to mefloquine treatment (50 in the first trimester), the drug was associated with an increased risk of stillbirth, when compared to women treated with quinine (OR: 4.72, 95% CI: 1.7-12.7), women exposed to other antimalarials (OR: 5.10, 95% CI: 2-13.1), or women who had no malaria (OR: 3.50, 95% CI: 1.6-7.6). Mefloquine was not associated with abortion, low birthweight, or malformations of the fetus [55]. In view of the published data, the current recommendations on the use of mefloquine for the treatment of malaria in pregnancy (avoid mefloquine unless there is a clear benefit for the mother) do not need to be changed. However, the outcome of pregnancies exposed to mefloquine should be documented whenever possible.
- Usefulness of mefloquine in the context of resistance: mefloquine is clearly an important antimalarial compound for the treatment of infections caused by *P. falciparum* resistant to other drugs. Combined to artesunate it has remained the first-line treatment of uncomplicated falciparum malaria in non-pregnant patients in Thailand for over 10 years. Given its toxicity profile (see above) it can be used in pregnancy in areas with a high risk of malaria where resistance to mefloquine is absent and where other drugs have lost their effectiveness. The drug long half-life (2-3 weeks) makes it a good potential candidate for chemoprophylaxis [16,102] and for IPT.

Dapsone in Combination with Chlorproguanil (Lapdap)

This drug is potentially an important antimalarial for *P. falciparum* in pregnancy but would be appropriate as first-line therapy only in combination with an artemisinin and providing safety and efficacy were acceptable.

- Pre-clinical studies, animal data: dapsone was not found to be teratogenic in animals even at high doses [44]. Proguanil and chloroproguanil were found to have no teratogenicity in rats, but cycloguanil, the active metabolite of proguanil, is toxic at the stage of cleavage of the ovum [103].
- Human data on toxicity in pregnancy: studies of dapsone in pregnant women with leprosy did not show an increase in the rate of abnormal outcomes. One case of neonatal hyperbilirubinemia following the maternal use of dapsone has been reported [104]. Dapsone is excreted in the breast milk in quantities potentially toxic for the newborn and should be avoided during lactation [105]. There were only 19 documented cases of exposure to dapsone in the first trimester identified [106-109].
- Clinical experience: in humans, proguanil (and chlorproguanil) is considered to be very safe and has been widely recommended and used daily for prophylaxis for over 40 years. A recent series of pharmacokinetic investigations indicated that pregnancy alters the metabolism of proguanil and that

current dosage recommendations may be inadequate [110-112]. This poses a delicate problem for fixed combinations such as chlorproguanil-dapsone, in which the dose of dapsone would have to be significantly increased. There is only one trial on the use of the combination in pregnancy in which 81 Kenyan pregnant women with *P. falciparum* malaria received a single dose of chlorproguanil (1.2 mg/kg) and dapsone (2.4 mg/kg). The combination was more effective than chloroquine (but provided a shorter protection than SP) and there were no adverse effects, although the outcomes of the pregnancies were not reported [25].

- Usefulness of chlorproguanil-dapsone in the context of resistance: the combination of chlorproguanil and dapsone, could prove very useful in areas of Africa where chloroquine resistance is established, but in principle it should be used in combination with artesunate. The increased risk of anaemia in glucose-6-phosphate dehydrogenase (G6PD) deficient patients could limit the use of chlorproguanil-dapsone in populations with a high prevalence of the trait. The combination of dapsone and pyrimethamine (Maloprim®) has been used for prophylaxis in the Gambia and no obvious toxicity to the mothers or fetuses was reported [113-116]. A recent review on the use of dapsone in pregnancy [117] concludes that currently available data on dapsone limit the extent to which a meaningful quantitative risk-benefit analysis can be made. Controlled trials have provided data on maternal tolerance and when used as an antimalarial drug in combination therapy, clear benefits in terms of improved birthweight were achieved.

Artemisinin Derivatives

The artemisinin derivatives are the most important innovation in the armamentarium against malaria. the drugs (mainly artesunate and artemether) are derived from the plant *Artemisia annua*. They are the most effective antimalarial known and there is no resistance to them as yet. These compounds have been extensively studied in animals and in humans and the experience in human pregnancy is encouraging. They cannot be used for prophylaxis or IPT because of their short half-life.

- Pre-clinical studies, animal data: Artesunate is very toxic to rat and rabbit embryos. Fetal resorption in rats has been reported with relatively low doses (28-223 mg/kg/d) given orally on days 9-14 of gestation [118]. In a more recent investigation artesunate was administered orally to mated females rats (24/grp) at doses of 0, 6, 10, or 16.7 mg/kg/day on Days 6-17 post-coitum. Totally resorbed litters were observed for 0, 4, 14 and 21 females, respectively. In addition, 2 of 20 litters at 6 mg/kg, and 3 of 9 litters at 10 mg/kg/day had fetuses with bent and/or shortened bones (scapula, humerus, radius, ulna, tibia, fibula, femur) compared with 1 of 23 control litters. Treatment-related heart defects (VSDs) also occurred in 6 of 20 litters at 6 mg/kg and 1 of 9 litters at 10 mg/kg/day, compared to 1 control litter [119]. Thus the animal studies (in rats and rabbits) have consistently shown severe embryo-fetal toxicity leading to a high resorption rate, with a steep dose-response curve as well as a low incidence of cardio-vascular malformations and skeleton abnormalities [120]. A recent study found that tissue damages in embryos exposed to DHA were attributable to inhibition of angiogenesis in the yolk sac [121], however the relevance of these findings to larger mammals is unknown.
- Human studies on toxicity in pregnancy: two early reports in the Chinese literature described the effects of artesunate, artemisinin or artemether in a small number of pregnant women. Li *et al.* studied 6 pregnant women (between 17 and 27 weeks of gestation) and Wang reported the outcome of 17 pregnancies. Neither found evidence of drug toxicity [122,123]. There were 94 cases of first trimester exposure to artesunate identified in the published literature [86,124] and no unexpected adverse effects were reported (see details below).
- Clinical experience: In a study involving 461 Karen pregnant women, McGready *et al.* recently described the side effects and the efficacy of two artemisinin derivatives (artesunate and artemether). There was no clinically significant adverse effect of the drugs, and the outcomes of the pregnancies, or the development (neurological and physical) of the infants, including 44 infants exposed during the first trimester (mean (sd) [range] gestation: 9.2 (3.0) [3-12.9] weeks) [124]. To date more than 980 pregnant women (including 108 in the first trimester) from the same community have received an artemisinin-based treatment with no increase in adverse outcomes (McGready, personal communication). Sowunmi *et al.* in Nigeria also found that artemether was safe in 45 pregnant women with resistant *P. falciparum* infections [125]. In a retrospective study following a mass treatment campaign in the Gambia (artesunate 4mg/kg and sulfadoxine-pyrimethamine), the outcome of pregnancy in 287 pregnant women was compared to 172 women who were not exposed [86]. There was no evidence of a teratogenic or otherwise harmful effect, and there was no difference in the proportion of abortions, stillbirths, or infant deaths among those exposed or not exposed to the drugs, including women exposed in the first trimester (n=50). Treatment with SP and artesunate during pregnancy was associated with higher birthweight, which may have resulted from clearance of malaria parasites, as placental malaria is associated with reduced birthweight [126]. However, the influence of confounding factors cannot be excluded.
- Usefulness of the artemisinin in the context of drug resistance: there is no documented *in vivo* or *in vitro* resistance to the artemisinin derivatives. However it is generally accepted that these compounds should be used in combination with another antimalarial in order to exert mutual protection against the development of resistant strains [127]. Potential candidate partner drugs that could be combined to an artemisinin derivative and used in pregnancy include,

amodiaquine, sulfadoxine-pyrimethamine, chlorproguanil-dapsone and in certain circumstances mefloquine, clindamycin (azithromycin), or atovaquone-proguanil. The first randomised control trial of artemisinin combination therapy in pregnancy was with mefloquine 15 mg/kg on day 1 and 10 mg/kg on day 2 and artesunate 4mg/kg daily for 3 days, was carried out on the Thai-Burmese border [53]. The 63 day PCR genotyping confirmed excellent cure rates 98.2% (95% CI: 94.7-100), and low gametocyte carriage rates 2.3% (95% CI: 0-11). The combination was better tolerated than quinine alone and there were no stillbirths or congenital abnormalities. In another study from the same area 27 women with multiple resistant infections were treated with the triple combination of atovaquone-proguanil-artesunate and followed until delivery. The treatment was well tolerated and there was no evidence of toxicity for the mothers and the fetus. All but one woman were cured (cure rate 96%; 95% CI 89 to 100%) [128]. However no other publications were identified which reported the use of such artemisinin combinations in pregnant women. The rapid emergence of resistance to SP in Africa will compromise the effectiveness of using this drug alone in intermittent treatment doses in prevention of malaria in pregnancy. Prospective evaluation of ACT is therefore urgently needed [129]. Recent conclusions from a World Health Organisation/Roll Back Malaria expert meeting on the use of artemisinin derivatives in pregnancy, stipulated that these drugs should be used in pregnant women with severe malaria and to treat uncomplicated malaria in the last 2 trimesters of pregnancy, if there is no other suitable drug available (i.e. when other drugs have become ineffective) [130]. There is agreement that the artemisinin derivatives should not be withheld at any stage of pregnancy, in cases of severe and complicated malaria, if the life of the mother is at risk. This is re-enforced by the recent observation that artesunate reduces mortality by more than 34% when compared to quinine in adults with severe malaria [131].

Atovaquone-Proguanil

This drug combination is a potentially valuable first-line antimalarial for management of *P. falciparum* malaria in pregnancy. Atovaquone (Mepron®) is an antiprotozoan agent used in the treatment of *Pneumocystis carinii* infection and in toxoplasmosis.

- Pre-clinical studies, animal data: the manufacturer (GlaxoSmithKline, Research Triangle Park NC) reports developmental toxicology testing in rats and rabbits. Maternal administration in rats resulted in fetal plasma concentrations of the parent drug and its metabolites of 18% and 60% of maternal plasma concentrations in mid- and late pregnancy, respectively. No adverse effects were seen in rat pregnancy at maternal plasma concentrations 2 to 3 times those recommended in humans. In rabbits, however, fetal weight and viability were decreased at maternal plasma concentrations of one-half those seen in humans. There was maternal toxicity at this concentration and it is possible that the fetal effects were partly or entirely due to the maternal toxicity. The concurrent fetal plasma concentrations were one-third those measured in the does. (GSK Reprotox database 5/2003). Pre-clinical studies did not indicate that the drug was toxic [132].
- Human data on toxicity in pregnancy: no publications have reported on toxicity of atovaquone in pregnancy.
- Clinical experience: in addition to the aforementioned atovaquone-proguanil-artesunate treated women, a further 24 Karen pregnant women have completed a pharmacokinetic study of atovaquone-proguanil (and artesunate) following recrudescent multi-resistant falciparum infections. The plasma levels of atovaquone and proguanil were approximately half and two thirds respectively of those observed in non pregnant patients with malaria. If used in pregnant women the dose of atovaquone-proguanil may need to be adjusted [111]. The combination is very susceptible to the selection of resistant mutants, as resistance to atovaquone is mediated by a single mutation on the cytochrome b gene of *P. falciparum.* It should therefore be protected by combination with an artemisinin derivative. An efficacy and tolerability study of this triple combination has been completed on the Thai-Burmese border and in total, 101 pregnant women have received this triple combination, without apparent toxicity [133].
- Usefulness in the context of drug resistance: unfortunately the use of this highly efficacious 3 day treatment for pregnant women with multiple drug resistant infections, will be compromised by its cost: >45 USD per treatment.

Lumefantrine (and Artemether)

This drug combination is potentially an important first-line therapy for *P. falciparum* malaria.

- Pre-clinical studies, animal data: in animal studies (Novartis data-on-file), lumefantrine was shown to be neither mutagenic, nor embryotoxic. Doses up to 1000 mg/kg have been tested and shown to be well tolerated, with no evidence of maternal or embryo-fetal toxicity. Additional studies were conducted with the combination (ratio 1: 6) of artemether and lumefantrine. In rats receiving doses of 0, 30, 100 and 300 mg/kg of artemether/lumefantrine, reduced maternal body weight and food consumption and a high level embryotoxicity occurred with doses greater than 100 mg/kg. Doses of the combination of artemether/lumefantrine of 30 mg/kg were neither embryotoxic or teratogenic. In rabbit studies, a more favourable profile was seen. Doses greater than 210 mg/kg of this combination were associated with embryo-fetal lethality. Viable fetuses, however, showed no abnormalities. Doses up to 105 mg/kg were free of treatment-induced effects. Artemether, however, showed maternal effects and embryo-fetal toxicity at 10 mg/kg in rats but no teratogenicity, with a no adverse effect level of 3 mg/kg. Similarly, embryo-fetal toxicity was documented in rabbits at 30

mg/kg, with no evidence of teratogenicity. The no-adverse effect level in rabbits was 25 mg/kg, which suggests a steep dose-response curve for embryotoxicity for this species. In summary, artemether, like all artemisinin derivatives, but not lumefantrine can induce fetal toxicity/resorption in the early days of gestation in rodents.

- Human data on toxicity in pregnancy: no published data available. Early gestational fetal toxicity/resorption would be very difficult to document in human pregnancy.
- Clinical experience: no published data available
- Usefulness in the context of drug resistance: potentially useful combination therapy whose value awaits the results of randomised therapeutic trials in pregnant women.

ANTIMALARIAL DRUGS THAT SHOULD NOT BE USED IN PREGNANCY

Halofantrine

Halofantrine is neither mutagenic nor teratogenic but is embryotoxic in animals. Pregnant rabbits exposed to high doses (60-120 mg/kg/d) between day 7 and 19 of gestation gave birth to pups with skeletal abnormalities. Body-weight was decreased in female rats exposed to 25-100 mg/kg/d of halofantrine from day 15 of gestation and day 21 postpartum, and the pups also showed a loss of weight [134]. No data exists on the use of halofantrine in pregnant women, but the cardiotoxicity of the drug has compromised its role in the treatment of uncomplicated falciparum malaria.

Tetracycline/Doxycycline

These antibiotics are used in combination with quinine or artesunate in areas of multi-drug resistance [135]. Their use in human pregnancy is associated with disturbances of bone growth of the fetus [136] and with irreversible teeth coloration when given in the third trimester and in infancy [137]. Congenital cataract has also been reported [138]. Furthermore, the hepatotoxicity of tetracycline is increased in pregnancy [139] and fatal fatty liver degeneration occurred when large doses were used [140].

Primaquine

This 8 aminoquinoline is not prescribed in pregnancy because of the risk of intravascular hemolysis in the mother and the fetus. This risk is linked to the dose administered and the degree of G6PD deficiency [141].

CONCLUSIONS

Although malaria is the most important parasitic disease of man there are very few studies of antimalarials in human pregnancy. Almost nothing is known on the pharmacokinetics (Box **1**), safety and efficacy of drugs used to treat pregnant women with malaria. This is because pregnant women, even though a highly susceptible group, are systematically excluded from clinical trials. As a result, there is very little evidence on which to base recommendations for the prevention and the treatment of malaria during pregnancy. There are data on antimalarials in animals (Table **2**) but their relevance to human is questionable. The problem is even more acute for the first trimester of pregnancy (when the risk of embryotoxcicity (Box **2**) is higher) and there are generally no agreed recommendations in the national policies for antimalarial drug choice in asymptomatic parasitaemic women in the first trimester of pregnancy. This absence of data on the safety of antimalarials in pregnancy is aggravated by the view that in areas of intense transmission (such as sub-Saharan Africa), pregnant women with malaria are asymptomatic and may not need to be treated. This situation needs to be addressed because of the evidence that malaria related maternal morbidity and mortality is rising in Africa and elsewhere, mainly because of drug resistance in addition to the aggravating effects of HIV infection [154]. Vector control measures have been shown to be beneficial to pregnant women in large field trials, but despite this protection, many women still become infected and require treatment. In addition, the increasing use of ACT in Africa will translate into the exposure (intentional or not) of more women to these drugs usually early in their pregnancy.

Box 1. Pharmacokinetics of Antimalarials in Pregnancy

The pharmacokinetics of antimalarials are altered in pregnancy. This is the consequence of multiple factors: expansion of the volume of distribution, increase in clearance, changes in the protein binding, lipid distribution and absorption of drugs, as well as influence of hormonal changes on the drug metabolism. These changes can result in lower plasma concentrations and AUCs and this can lead to reduced efficacy.

Few studies have been published. Chloroquine in treatment [142] and as prophylaxis [18], but also proguanil [112] and atovaquone [111], as well as dihydroartemisinin [155] all have altered kinetics in pregnancy, and plasma levels are significantly lower than in non-pregnant patients with malaria. This is likely to be due to increased clearance, larger volume of distribution and perhaps altered absorption. It is clear that dosage of these (and probably other) antimalarials need to be adapted when given to pregnant women.

There is a very urgent need to assess the safety and the efficacy of alternative treatments in pregnancy, and these include the artemisinin based combination therapies. Animal studies are the first step to risk assessment, but considerable information on kinetics and mechanisms of action are required in order to assess the extent to which the results of animal studies are relevant to humans. The pharmacokinetics of most antimalarial drugs are modified in pregnancy and dosages need to be adapted. Other factors such as maternal HIV status, interactions with antiretrovirals and other drugs, the use of haematinics and host genetic polymorphisms may influence antimalarial drug efficacy and disposition and require further studies. To date there has been no study examining HAART-antimalarial interactions in pregnancy.

The choice of drugs to treat malaria during pregnancy will depend on the trimester and on the regional pattern of resistance to antimalarials. Despite the paucity of data, quinine (with or without clindamycin) and artemisinin combination treatment (ACT) are now recommended for therapeutic use in Africa, and elsewhere and are summarized in Table **3**.

Table 2. Summary of Adverse Effects in Animals of Antimalarial Drugs in Pregnancy

Antimalarial human dose	Embryotoxicity	Teratogenicity	CNS	Skeletal and growth	Other
Chloroquine **25 mg/kg over 3 days**	**A:** Rat **D:** 1000 mg/kg dose **E:** embryonic death in 27% [143]; embryotoxic and dysmorphogenic [144,145]	**A:** Rat **D:** 1000-mg/kg dose **E:** anophthalmia, microphthalmia in 47% of the surviving fetuses [144]	**À:** Rat embryo culture **E:** inhibited cranial neural tube [143,144]; altered morphology of cranial neural crest cells [143] Microophthalmia and abnormal otic primordium [145] Accumulation in the eyes in early gestation and eyes and ears in later pregnancy [3]	**A:** Rat **E:** growth retardation; skeletal dysmorphism [146]. **A:** Chicken embryo **E:** short and crooked neck; muscular hypoplasia of legs [147]	**A:** Rat **D:** 40 mg/kg **E:** retarded fetal lung maturation; reduction of saccular expansion [1]
Quinine **10 mg/kg per day for 7 days.**	**A:** Rat **E:** No effect observed in rat embyo-toxicity studies [39]	**A:** Rat [39,143], rabbit [143] and dog [37], macaque monkey **D:** quinine hydrochloride (20-200 mg/kg daily) on days 27-29 of gestation [40]. **E:** No fetal abnormalities **A:** rats exposed in pre-gestative and gestative periods **D:** quinine sulfate in water (0.25 mg/ml) **E:** Congenital malformations reported in 5% [38]	**A:** Pups nursed on rats **E:** maturation retardation [38]	**A:** Rat **E:** mean birth weights significantly lower compared to pups born to control rats [38]	**A:** Rat **D:** up to 200 mg/kg/day **E:** No interference with auditory function in rats [39]
Sulfadoxine	**A:** rat **D:** Sulfamoxole (500 mg/kg) **E:** no embryotoxic effects [148]	**A:** Rat: **D:** high doses (100-1000 mg/kg/day) **E:** teratogenic [73]		**A:** rats exposed from day 9 to 14 of gestation **E:** Cleft palate [73].	
Pyrimethamine	**A:** Rat: **D:** Dose related effects: 12.5 mg/kg given daily for 3 consecutive days resulted in 31% live fetuses; 2 daily doses 66% survival, and at 0.3 mg/kg on 10 consecutive days 94% survived. Equivalent human doses resulted in no adverse effects [150] **E:** embryotoxic, causing fetal resorption and growth retardation [149] embryotoxicity increased with combination of pyrimethamine and folic acid, but prevented by the use of folinic acid [76,151]	**A:** Rat **E:** teratogenic, in some cases, similar to the human dose [152]	**A:** Rat: neural tube defects [152]	**A:** Rat **E:** cleft palate, mandibular hypoplasia, limb defects [152]	**A:** Rat **E:** at slightly higher doses pyrimethamine caused chromosomal aberrations such as trisomy or chromosomal mosaicism [152]

(Table 2) contd…..

Antimalarial human dose	Embryotoxicity	Teratogenicity	CNS	Skeletal and growth	Other
Combination: **Sulfadoxine-pyrimethamine**	**A:** Rat **D:** Limited, dose-dependent; therapeutic doses (0.72 mg/kg) intra-muscularly, day 5-12 and 19 of gestation **E:** embyotoxicity [44]; complete embryo resorption [77]	**E:** Teratogenic - effect 2 fold higher than expected from the summation of each drug effect [44]		**A:** Rat **E:** cleft palate [44]	
Mefloquine	**A:** Rabbit **D:** 160 mg/kg/OD [44] **E:** Embryotoxic [97] Fetal resorption [44]	**A:** mice, rats, rabbits **D:** At high doses (80–160 mg/kg/day) **E:** teratogenic [44]		**A:** Rat **D:** 100 mg/kg/daily **E:** Skeletal, soft tissue malformation and growth retardation [44]	**A:** Rat **D:** Smaller doses (20–50 mg/kg/day) **E:** impair fertility in rat (Hoffman La Roche, Product information)
Dapsone		**D:** high doses **E:** not teratogenic			**A:** Pregnant and lactating mice and rats: **D:** Maximum maternally tolerated dose (100 mg/kg), twice in late gestation and 5 times a week during lactation and then continued in offspring after weaning. (usual human dose 50–300 mg/d) **E:** Small but significant increase in tumours was noted [152]
Proguanil and chlorproguanil	Cycloguanil, the active metabolite of proguanil, toxic at stage of cleavage of the ovum [109]	**A:** Rat: **E:** None [109]			
Artemisinins	**A:** Rat: **D:** relatively low oral doses (28-223 mg/kg/d) on d 9-14 of gestation **E:** fetal resorption, limited and stage specific in gestation [118]			**A:** rats and rabbits **E:** low incidence of heart defects, skeletal defects (rat only); sensitive developmental periods (rat) determined [119,120]	
Atovaquone-proguanil		No formal studies but no indication of toxicity [132]			

(Table 2) contd…..

Antimalarial human dose	Embryotoxicity	Teratogenicity	CNS	Skeletal and growth	Other
Halofantrine	**A:** Rabbit **D:** high doses, 60-120 mg/kg/d, between d 7-19 gestation **E:** embryotoxic [134]	None reported [134]		**A:** Rabbit pups **E:** skeletal abnormalities [130]. **A:** pups of female rats **D:** 25-100 mg/kg/d, d 15 gestation - d 21 postpartum **E:** Decreased body-weight of female,weight loss pups [134]	
Tetracycline /Doxycycline	Not observed		**A:** Rat **E:** lens discolouration [137]	**A:** Chick embryo **E:** abnormal skeletal development, reduced fetal growth [136]	
Lumefantrine	Not observed	Not observed			

A: animal; **D:** dose; **E:** effect.
Chloroquine, primaquine and amodiaquine shown to be mutagenic and genotoxic [27].

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Box 2. Animal Toxicity

Definitions:

Embryo: The definition of embryo is the same in animals and humans. The corresponding periods in animals to those given in man, are Mouse day 6-15 of gestation (duration 19 days); Rat day 6-16 of gestation (duration 22 days); Rabbit day 6-18 of gestation (duration 30-32 days). There are slightly different values in different sources, because there is no clear endpoint for the change from the embryonic to fetal period. In animals, the fetal period covers those derivatives of the fertilized ovum that eventually become the offspring, during their period of most rapid development, i.e., after the long axis appears until all major structures are represented. In man, the developing organism is an embryo from about two weeks after fertilization to the end of seventh or eighth week.

Fetus: A developing unborn offspring of an animal that gives birth to its young (as opposed to laying eggs). From approximately three months after conception the offspring take on a recognisable form (all parts are in place, etc.). In human development, the period after the seventh or eighth week of pregnancy is the fetal period.

Embryotoxicity: Injury to the embryo, which may result in death or in abnormal development of a part. Substances can be embryotoxic by an action at several sites, eg directly on the embryo, on the placenta (in the different forms this has in different animals and at different stages of gestation), on the utero-placental blood flow, or on the mother acting on the hormonal control of gestation. The latter is very important as hormonal control of pregnancy in rodents is very different from that in humans. Drugs which cause complete embryofetal loss in rodents, like the artemisinins, may act on the rodent pituitary to affect hormone secretion, causing complete resorption by a mechanism which does not operate in humans.

Most people now use the term 'embryofetal toxicity' rather than embryotoxicity to cover effects at both stages of development. The commonest form is reduced fetal bodyweight or birthweight which are induced during the fetal period.

Teratogenicity: The ability to cause defects in a developing fetus. This is distinct from mutagenicity, which causes genetic mutations in sperms, eggs or other cells. Teratogenicity is a potential side effect of many drugs, such as thalidomide. Strictly speaking, this is defined as the ability to cause structural defects in a developing embryo or fetus. As functional defects are of importance (e.g. effects on the CNS causing mental retardation, for example alcohol), the term 'developmental toxicity' is preferred rather than teratogenicity, and covers both structural and functional deficits. Teratogenicity is still used if only structural defects are described. Developmental toxicity tests also include treatment in lactating mothers during the postnatal period, since the CNS is still developing at this time (up to 18 months in humans or 1 month in rats).

Table 3.

Uncomplicated falciparum malaria	**First trimester:** • First episode: Quinine 10 mg/kg three times a day for 7 days with or without Clindamycin 5 mg/kg three times per day for 7 days. • Subsequent episodes: ACT locally effective or artesunate 2 mg/kg/d for 7 days with Clindamycin as above. **Second and third trimesters:** • First episode: ACT locally effective or artesunate plus clindamycin as above. • Subsequent episodes: artesunate plus clindamycin as above. • Or quinine plus clindamycin as above. **Prevention:** IPT with SP where efficacy remains.
Severe malaria	Artesunate 2.4 mg/kg IV at hour 0, 12 and 24 and continued every 24 hours until the patient can tolerate oral artesunate 2 mg/kg/dose, for 7 days and clindamycin 5 mg/kg three times daily for 7 days. OR Quinine i.v: Loading dose (LD) 20 mg/kg given over four hours, then 10 mg given 8 hours after the LD was started, followed by 10 mg/kg every 8 hours for 7d. Once the patient has recovered sufficiently to tolerate oral medication both quinine 10 mg/kg and clindamycin 5 mg/kg, three times daily should be continued daily for 7 days.
Non-falciparum malaria	Chloroquine phosphate (1 tablet contains 250 mg salt, equivalent to 155.3 mg base). Dose is 10 mg/kg base once a day for 2 days followed by 5 mg/kg base on third day. For chloroquine resistant *P. vivax* amodiaquine, quinine, mefloquine, artemisinin derivatives can be used. Prevention: chloroquine phosphate 300 mg on admission followed by 150 mg per week.

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